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Urinary 11-dehydro-thromboxane B₂ is associated with cardiovascular events and mortality in atrial fibrillation patients.

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Running title: Urinary thromboxane B₂ and Atrial fibrillation.

Key words: atrial fibrillation, 11-dehydro-thromboxane B₂, cardiovascular diseases, mortality

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Abstract

BACKGROUND: Non-Valvular Atrial Fibrillation (AF) patients show high residual cardiovascular risk despite oral anticoagulants. Urinary 11-dehydro-thromboxane B₂ (TxB₂) is associated with an increased risk of cardiovascular events (CVEs), but its predictive value in anticoagulated AF patients is unknown.

METHODS: Prospective single-center cohort study, including 837 AF patients. Mean time of follow-up was 30.0 months yielding 2062 person-years of observation. Urinary 11-dehydro-TxB₂ was measured at baseline. The primary end-point was the occurrence of a CVE including fatal/nonfatal myocardial infarction (MI) and ischemic stroke, transient ischemic attack, cardiac revascularization and cardiovascular death.

RESULTS: Mean age of patients was 73.1 years, and 43.6% were **women**. Median 11-dehydro-TxB₂ levels were 100 [IQR 50 -187] ng/mg of urinary creatinine. Overall, the anticoagulation control was adequate (63.9% of mean time in therapeutic range). A CVE occurred in **99** (11.8%) patients, 55 were CV deaths. At baseline, 11-dehydro-TxB₂ levels were higher in patients with a CVE compared to those without (186 [107-400] vs. 98 [52-170], $p<0.001$). An increased rate of CVEs (Log-Rank test, $p<0.001$) and CV deaths ($p<0.001$) was observed across tertiles of 11-dehydro-TxB₂.

CVEs were associated with age (Hazard Ratios [HR]: 1.72 per 1SD, 95% Confidence Interval [CI] 1.33 -2.21, $p<0.001$), diabetes mellitus (HR: 1.89 95%CI 1.20-2.96, $p=0.005$), heart failure (HR: 1.60, 95%CI 1.01-2.54, $p=0.044$), history of stroke/transient ischemic attack (HR: 1.96, 95%CI 1.25-3.06, $p=0.003$) and 11-dehydro-TxB₂ (HR: 1.64 per 1 SD, 95%CI 1.42-1.89, $p<0.001$).

CONCLUSIONS: Urinary 11-dehydro-TxB₂ levels are associated with a residual risk of CVEs and CV mortality in AF patients despite anticoagulant treatment.

Author Contributions

Violi, Pignatelli and Pastori had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors

Acquisition of data: Pastori, Bartimoccia, Carnevale, Vicario, Bucci, Nocella

Adjudication of outcomes: Pignatelli, Violi, Cangemi

Analysis and interpretation of data: Pastori, Farcomeni

Drafting of the manuscript: Pastori, Pignatelli, Hiatt; Lip, Violi

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Farcomeni, Pastori

Obtained funding: Pignatelli

Study supervision: Hiatt, Lip, Violi

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia that is associated with a high risk of cardiovascular events and increased morbidity and mortality.¹ Ischemic cardiovascular events are primarily localized in the cerebral circulation, where AF is particularly associated with ischemic stroke². Indeed, ischemic stroke related to AF is more severe, with a greater mortality and morbidity due to disability and longer hospital stays³.

AF patients are characterized by various atherosclerotic risk factors including arterial hypertension and coronary artery disease, resulting in a high risk of myocardial infarction (MI).^{4, 5} Indeed, amongst elderly AF patients with high CHA₂DS₂-VASc score, the risk of MI is similar to that of stroke⁶. For this reason, AF patients are often treated with a combination of oral anticoagulants (OACs) and aspirin, which inhibits platelet thromboxane A₂. Despite an unclear evidence of meaningful net clinical advantage,⁷ a large number of AF patients are often treated with OACs and aspirin, resulting in an associated high risk of serious bleeding.⁸ Recent registry data (ORBIT-AF)⁹ reported that a combination of OACs with aspirin was observed in 35% of patients but the rationale for the use of such a combination was unclear. In more than one third, there was no evidence of any atherosclerotic disease, suggesting poor definition of potentially 'high risk' candidates for combination therapy with OACs plus aspirin.

Urinary levels of 11-dehydro-thromboxane B₂ (TxB₂), a stable metabolite of thromboxane A₂, are a reflection of thromboxane A₂ body generation¹⁰ and its inhibition by aspirin.¹¹ Previous studies in patients at risk, or with previous cardiovascular events (CVEs) have shown that urinary 11-dehydro-TxB₂ levels are **associated with** CVEs including stroke, MI and cardiovascular deaths, suggesting that this biomarker may identify patient categories in which suppression of thromboxane A₂

generation is of potential clinical benefit.¹² Until now, **the** value of measuring urinary 11-dehydro-TxB₂ in anticoagulated patients with AF is unknown.

We hypothesized that urinary 11-dehydro-TxB₂ levels could be useful to identify AF patients on OACs who are at high residual risk of cardiovascular events. To evaluate this hypothesis, we performed a prospective cohort study in which the relationship between urinary 11-dehydro-TxB₂ and cardiovascular events was investigated in anticoagulated AF patients, who underwent a mean follow-up of 30.0 months. Second, we also assessed the clinical factors **associated with** urinary 11-dehydro-TxB₂ levels.

Materials and Methods

Study design and patient selection.

This prospective single-center cohort study included 950 patients with AF who were referred to the Atherothrombosis Center of the Department of Internal Medicine and Medical Specialties of Sapienza-University of Rome from February 2008 to October 2013. Included patients received oral vitamin K antagonists according to the CHA₂DS₂-VASc score.¹³ International normalized ratio was maintained in a therapeutic range of 2.0–3.0 and time in therapeutic range (TTR) was calculated. Patients taking warfarin and an antiplatelet drug were eligible.

Exclusion criteria at baseline included: presence of prosthetic heart valves, cardiac stent placement in the previous year, severe cognitive impairment, chronic infectious diseases, autoimmune systemic diseases and active cancer. Patients treated with antiplatelet agents alone were also excluded, as well as patients with a cardiac revascularization in the previous year.

At enrollment, medical history and anthropometric data were recorded and a sample of urine was collected from all patients. Arterial hypertension was defined as elevated blood pressure ($\geq 140/\geq 90$ mmHg) or taking antihypertensive therapy;¹⁴ diabetes mellitus as a random plasma glucose ≥ 200 mg/dl, or fasting plasma glucose ≥ 126 mg/dl, or use of anti-diabetic treatment.¹⁵ Heart failure was defined as the presence of signs and symptoms typical of heart failure or reduced ejection fraction ($\leq 40\%$).¹⁶

Follow-up

All patients were followed-up for the entire duration of the study and outcome events were recorded. Patients were regularly seen at each control for INR monitoring every 20-40 days at the Atherothrombosis Center. Patients missing INR control were contacted and information about vital status and hospitalizations were recorded. Follow-up data were obtained by review of

hospital databases, medical records, death certificates, telephone interviews or general practitioners.

Outcome Events. The occurrence of CVEs was considered as the primary outcome of the study. CVEs included fatal and nonfatal ischemic stroke, fatal and nonfatal MI, transient ischemic attack (TIA), cardiac revascularization/coronary artery bypass surgery and cardiovascular death. Diagnosis of MI was made according to the international definition.¹⁷ The occurrence of ischemic stroke was determined on clinical manifestations and confirmed by radiological findings; TIA was defined according to the Classification of Cerebrovascular Diseases III.¹⁸ If a patient died within 4 weeks of stroke or MI, this event was recorded as fatal stroke or fatal MI. Cardiovascular death included sudden death; progressive congestive heart failure; procedure related death (surgical or percutaneous revascularization); and presumed cardiovascular deaths (i.e. those for which a non-cardiovascular cause had not been clearly established). Only the first event that occurred during follow-up was used in the analysis. Bleeding events were classified according to the International Society on Thrombosis and Haemostasis.¹⁹

Adjudication of outcomes. Data on CVEs were prospectively collected during follow-up. When a CVE occurred, a standardized form was filled in by the investigators. Details on CVEs were registered, as well as death certificates, hospital discharge letter or copy of the medical records of hospitalization, and other clinical documentation (i.e. radiology and laboratory data) were also obtained from patients, or in case of death, from relatives of patients or from general practitioner. Adjudication of cardiovascular events was performed by a committee composed by three physicians (FV, PP, RC) who did not participate to the recruitment of patients and was unaware of the clinical and laboratory characteristics of any enrolled patient. Each member of the committee independently evaluated and adjudicated CVEs in a blinded manner. **In case of discordant evaluation, adjudication of an event was made after a shared review of available clinical data.**

All patients provided a written informed consent. The study protocol was approved by the local ethical board of Sapienza-University of Rome and was conducted according to principles of the Declaration of Helsinki²⁰. **This work was supported by Sapienza University of Rome, Grant Code “Pignatelli Progetto Ricerca Sapienza 2011”. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.**

Laboratory analyses. The concentration of urinary 11-dehydro-TxB₂ was measured by an ELISA commercial kit (Cayman). Data are expressed as ng/mg creatinine. Intra- and inter-assay coefficients of variation were 4.0% and 3.6%, respectively. Analyses were performed in a blinded manner. Thus, the biologist (RC) who analyzed the samples was not aware of clinical characteristics of AF patients, or of CVEs. Moreover, 20% of samples were randomly selected and re-analyzed by a second biologist (SB), and results were compared by a third one (CN).

Statistical analysis. Categorical variables were reported as counts (percentage). Following a test of statistical normality, continuous variables were expressed as mean \pm standard deviation (SD) or median and interquartile range (IQR) unless otherwise indicated. Independence of categorical variables was tested with the χ^2 test. The normal distribution of parameters was assessed by Kolmogorov–Smirnov test. Student unpaired t test and Pearson product-moment correlation analyses were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney U test and Spearman rank correlation test) were used for all the other variables. Group comparisons were performed using Fisher’s F-test (ANOVA) or Kruskal-Wallis test when needed. After dividing the AF population into tertiles according to urinary 11-dehydro-TxB₂ values, univariate analyses comparing clinical characteristics among tertiles of 11-dehydro-TxB₂ was performed. The cumulative incidence was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test. The association

between tertiles of 11-dehydro-TxB₂ levels and outcomes was examined for both CVEs and CV deaths separately. Cox proportional hazards analyses were used to calculate the adjusted relative hazards of CVEs and CV deaths by each clinical variable. **The multivariable analyses were determined including pre-specified variables and using urinary 11-dehydro-TxB₂ as continuous variable. Thus, in addition to 11-dehydro-TxB₂ levels, the following variables were entered as covariates: age, smoking, arterial hypertension (treated), diabetes, history of MI, history of stroke/TIA, heart failure, treatment with antiplatelet agents and statins.**

Risk prediction metrics. Calibration was assessed by comparing predicted and expected events at each time point. Discrimination and risk reclassification were assessed by means of C-index, difference in C-index with a model without TxB₂, and Integrated Discrimination Improvement (IDI) index for censored data.^{21, 22} **The proportionality of hazards assumption for the Cox model has been checked using plots of Schoenfeld residuals.**

Finally, we used B-splines to identify a threshold according to Molinari et al.²³, but no threshold was detected.

P values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, SPSS Inc. and R version 2.15.2).

Sample size calculation. The sample size was planned using a log-rank test for comparing the first and third tertile of urinary 11-dehydro-TxB₂. We planned a power of 80% and a type-I error rate of 5% and a difference in the rate from 0.93 to 0.85. Therefore, 53 events in the first and last tertile combined were planned in order to guarantee the prescribed power.

Results

Of the 950 AF patients screened, 20 patients refused to be included in the study. Based on the above-mentioned exclusion criteria, 71 patients were excluded and 22 patients were lost at follow-up. Thus, 837 AF patients were finally included in the study cohort. All patients were followed for a mean time of 30.0 (± 21.5) months, yielding 2064 person-years of observation. Mean age was 73.1 \pm 8.6 years, 43.6% were women. Median CHA₂DS₂-VASc score was 3 [2-4] (table 1). Overall, the mean TTR was adequate (63.9 \pm 17.1%). In the whole cohort, median 11-dehydro-TxB₂ levels were 100 [IQR 50 -187] *ng/mg of urinary creatinine*.

Correlates of urinary 11-dehydro-TxB₂ levels

To better stratify AF patients, we divided our study cohort into three groups based to tertiles of 11-dehydro-TxB₂ levels: <70 ng/mg creatinine for first tertile, 70-150 ng/mg creatinine for the second tertile and >150 ng/mg creatinine for the third tertile.

As shown in table 2, a significant difference among tertiles of urinary 11-dehydro-TxB₂ was found for CHA₂DS₂-VASc score, HAS-BLED score and use of β blockers agents. No difference in TTR was detected among *the tertiles of urinary 11-dehydro-TxB₂*.

Multivariable stepwise linear regression analysis of **factors associated with** logarithm of urinary 11-dehydro-TxB₂ demonstrated that history of MI was **positively** associated with 11-dehydro-TxB₂ levels ($\beta=0.11$, $p=0.006$), whilst antiplatelet use was inversely associated ($\beta=-0.10$, $p=0.012$). **All other factors were not significant.**

Relationship to outcomes

A CVE occurred in 99 patients (11.8%): non-fatal MI in 11, stent/CABG in 15, ischemic non-fatal stroke in 16, TIA in 2, and cardiovascular deaths in 55 (including 12 fatal MI and 6 fatal ischemic strokes). Table 1 depicts the clinical characteristics of the study cohort, in relation to

presence/absence of CVEs. Mean TTR was non-significantly lower in patients with and without CVEs (Table 1). Those sustaining CVEs were older, with more diabetes, heart failure, a clinical history complicated by cardiac and cerebrovascular events and higher CHA₂DS₂-VASc score (Table 1).

Urinary 11-dehydro-TxB₂ levels were higher in patients with CVEs during the follow-up ($p<0.001$) (Table 1). Similarly, urinary 11-dehydro-TxB₂ levels were significantly higher in patients with cardiovascular death (186 [120-387] vs. 100 [55-180] ng/mg of urinary creatinine, $p<0.001$). Kaplan-Meier analysis demonstrated a significantly increased rate of CVEs (Log-Rank test: $p<0.001$, Figure 1) and cardiovascular deaths (Log-Rank test: $p<0.001$) across tertiles of 11-dehydro-TxB₂. Thus, 13 CVEs occurred in the first, 24 in the second, and 61 in the third tertile of 11-dehydro-TxB₂.

Using a Cox proportional hazards analysis (table 3, panel A), CVEs were associated with age (Hazard Ratios [HR]: 1.72 per 1SD, 95% Confidence Interval [CI] 1.33 -2.21, $p<0.001$), diabetes mellitus (HR: 1.89 95%CI 1.20-2.96, $p=0.005$), heart failure (HR: 1.60, 95%CI 1.01-2.54, $p=0.044$), history of stroke/TIA (HR: 1.96, 95%CI 1.25-3.06, $p=0.003$) and urinary 11-dehydro-TxB₂ (HR: 1.64 per 1 SD, 95%CI 1.42-1.89, $p<0.001$).

When we analyzed only CV deaths (table 3, panel B), we found that age ($p<0.001$), diabetes mellitus ($p=0.004$), history stroke/TIA ($p=0.022$), and urinary 11-dehydro-TxB₂ ($p<0.001$) were positively associated with the outcome. Conversely, statin use was inversely associated with CV death ($p=0.037$).

Risk prediction metrics

Cardiovascular events. In order to assess calibration we compared observed vs. predicted CVEs at each time point (Figure 1, supplemental material). The goodness of fit is very good, and the line is not significantly different from the 45 degrees line ($p=0.64$). The C-index for the Cox model

without TxB₂ is 0.70, while including TxB₂ increased it to 0.76. IDI for TxB₂ was computed as 0.06 (p=0.007, 95%CI: 0.01 - 0.13).

Cardiovascular deaths. In order to assess calibration we compared observed vs. predicted CV deaths at each time point (Figure 2, supplemental material). The goodness of fit is very good, and the line is not significantly different from the 45 degrees line (p=0.86). The C-index for the Cox model without TxB₂ is 0.75, while including TxB₂ increased it to 0.80. IDI for TxB₂ was computed as 0.08 (p=0.019, 95%CI: 0.01 - 0.17).

Bleeding events

During follow-up, 105 hemorrhages (27 major and 78 minor) occurred. Patients who experienced a bleeding event had *lower values* of urinary 11-dehydro-TxB₂ (87 [49-136] vs. 100 [59-183]; p=0.025) and, as expected, a higher mean HAS-BLED score (2.0±0.96 vs. 1.69±0.94; p=0.02). A significant inverse correlation between HAS-BLED score and 11-dehydro-TxB₂ levels was found (r: -0.11, p=0.002). After dividing population according to tertiles of urinary 11-dehydro-TxB₂ values, a non-significant trend in the proportion of patients who bled was observed: 21.4% patients in the first, 19.9% in the second and 12.6% in the third tertile (p=0.052 among groups). The difference was significant, when we compared the first to the third tertile (p=0.013). Kaplan-Meier analysis showed a significant inverse rate of bleeding events across tertiles of urinary 11-dehydro-TxB₂ (**Log-Rank test, p=0.024**).

Discussion

This study provides novel data that urinary 11-dehydro-TxB₂ is associated with cardiovascular events in anticoagulated AF patients.

Previous studies have shown that urinary 11-dehydro-TxB₂ levels are predictive of cardiovascular events in patients at risk of athero-thrombotic complications.¹² In a secondary prevention trial,¹² a nested case-control study comparing patients who experienced or not cardiovascular events found that urinary 11-dehydro-TxB₂ levels were predictive of the risk of MI and cardiovascular death. This finding was confirmed in the CHARISMA trial,²⁴ which found that urinary 11-dehydro-TxB₂ levels were associated with an increased risk of stroke, MI or cardiovascular death.²⁴

In our study, we measured baseline urinary 11-dehydro-TxB₂ levels and analyzed the relationship between this variable and vascular outcomes during a follow-up of about 3 years. All patients included in the study were at high risk of stroke as evident by the high CHA₂DS₂-VASc score, and were on good quality anticoagulation control, as reflected by the average TTR.²⁵ As expected, a residual vascular risk remained, and the annual rate of cerebrovascular events in our study was 1.1% per year, which is similar to that reported in recent clinical studies.^{9, 26} Furthermore, 1.7% patients/year suffered from MI and cardiac revascularization, which is consistent with Roldàn et al.²⁷, who found a rate MI of 1.83%/year, and apparently in contrast with recent clinical trials with non-vitamin K oral anticoagulants (NOACs). In particular, the annual rate of MI is about 1% (ranging from 0.53%/year in the RE-LY trial²⁸, to 1.1%/year in the ROCKET AF study²⁹) in AF patients treated with warfarin, and even lesser in those treated with NOACs (from 0.53%/year in the ARISTOTLE trial³⁰ to 0.9%/year in the ROCKET AF study²⁹). The reason for this difference cannot be fully established at the moment, but different populations' age may account for this. Thus, the average age of our population is relatively higher than that reported in the trials with

NOACs, which is consistent with a previous study indicating that age >75 years is a risk factor for MI in AF³¹.

While we confirm previous data on the association between urinary 11-dehydro-TxB₂ levels and cardiovascular events, the novelty of the present study is our demonstration that urinary 11-dehydro-TxB₂ levels were associated with an increased risk of CVEs and cardiovascular death in an AF cohort already on OACs. Whilst urinary 11-dehydro-TxB₂ levels do not fully reflect platelet-thromboxane A₂ formation,³² this finding may suggest a potential role for platelets promoting vascular complications in some AF patients despite being on adequate OACs. Among the predictors of urinary 11-dehydro-TxB₂ levels, previous history of cardiac events was associated with urinary 11-dehydro-TxB₂ levels suggesting a potentially major interplay between coronary heart disease (CHD) and platelet activation in AF.

Analysis of the relationship between 11-dehydro-TxB₂ levels and bleeding showed that higher urinary 11-dehydro-TxB₂ levels were associated with lower risk of bleeding; accordingly an inverse association between HAS-BLED and urinary 11-dehydro-TxB₂ was detected. This is in contrast with a previous finding showing a direct relationship between urinary 11-dehydro-TxB₂ and bleeding, but different populations and designs do not allow a direct comparison of these data.²⁴ The biologic plausibility of our finding is in the probable inverse association between platelet activation and bleeding risk.

The study has clinical implications and limitations. **The present study would suggest that in AF on adequate oral anticoagulation, persistent platelet activation, as assessed by urinary 11-dehydro-TxB₂, is associated with vascular events. Patients with a clinical history of CHD were associated with enhanced urinary 11-dehydro-TxB₂** suggesting that AF patients with previous CHD is a subset which could benefit from warfarin in combination with antiplatelet treatment. However, a

recent retrospective study on this specific sub-setting denied this possibility as no beneficial effect but a higher risk of bleeding has been observed in AF patients treated with warfarin plus aspirin³³. Statins may represent an interesting option to be investigated as they possess antithrombotic effects by interfering with clotting system and, overall, by lowering platelet 11-dehydro-TxB₂^{34, 35}. Notably, statins reduce the risk of cardiovascular events in primary and secondary prevention trials^{36, 37} and could be therefore useful in combination with warfarin to reduce the residual cardiovascular risk in patients with AF. Randomized study is, however, necessary to investigate the effectiveness of warfarin plus statins in patients with AF. Finally, inhibitor of TxB₂ receptors^{38, 39} may represent another option in which this drug category could be investigated on top of oral anticoagulants.

Whilst this was a prospective study, it was conducted in a single Italian center, including patients with average age >70 years and a coexistence of a serious vascular risk profile. **Other limitations of this study include the relatively low number of patients and CVEs, the potential for residual confounding, the observational study design with the resulting inability to establish causal relations, the uncertain generalizability to other races/ethnicities.** A last limitation is the lack of a control group of patients with similar characteristics but without AF.

In conclusion, urinary 11-dehydro-TxB₂ levels is associated with residual risk of cardiovascular events in anticoagulated AF patients. Such association is particularly evident in AF patients with a history of coronary heart disease, who, therefore, may be potential candidates for additional antithrombotic strategies as part of the holistic approach to managing this common arrhythmia⁴⁰.

Conflict of Interest/Disclosures: None.

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Figure legend

Figure 1. Kaplan-Meier curves estimate of cardiovascular events according to tertiles of 11-dehydro-thromboxane B₂ levels.

Table 1. Baseline characteristics of the study cohort and according the occurrence of cardiovascular events.

	Whole cohort n=837	Cardiovascular events		p value
		No (n=738)	Yes (n=99)	
Age (years)	73.2±8.5	72.9±8.6	75.5±7.4	0.001
Women (%)	43.6	44.0	40.4	0.52
Body mass index (kg/m ²)	27.2±4.7	27.2±4.7	27.3±4.2	0.88
Smokers (%)	9.9	9.8	11.1	0.72
CHA ₂ DS ₂ -VASc score [#]	3 [2-4]	3 [2-4]	4 [3-5]	<0.001
Time in therapeutic range (%)	63.8±17.2	64.2±17.2	59.3±16.5	0.09
Urinary 11-dehydro-TxB ₂ [#]	100.0 [56.5-181.0]	98.0 [51.0-170.0]	185.0 [109.0-400.0]	<0.001
HAS-BLED score [#]	2 [1-2]	1 [1-2]	2 [1-2]	0.60
Arterial Hypertension (treated) (%)	92.8	92.5	94.9	0.53
Diabetes mellitus (%)	19.8	18.4	30.3	0.007
Heart failure (%)	17.7	15.7	32.3	<0.001
History of stroke/TIA (%)	16.7	15.0	29.3	0.001
History of MI/ Cardiac Revascularization (%)	24.0	22.4	36.4	0.004
Anti-platelets (%)	7.0	7.3	5.1	0.53
Statins (%)	37.4	37.4	37.4	0.99

CVEs: cardiovascular events, MI: myocardial Infarction, TIA: transient ischemic attack, TxB₂: thromboxane B₂

[#]data expressed as median and interquartile range.

Table 2. Baseline characteristics according to tertiles of urinary 11-dehydro-thromboxane B₂

	1st tertile (<70 ng/mg creatinine)	2nd tertile (70-150 ng/mg creatinine)	3rd tertile (>150 ng/mg creatinine)	P value 1st vs. 3rd
Age (years)	72.8±8.0	73.6±8.8	73.2±8.6	0.56
Women (%)	39.1	45.7	45.8	0.19
Body mass index (kg/m²)	27.1±4.5	27.2±4.6	27.4±4.9	0.74
Smokers (%)	12.2	7.9	9.8	0.24
CHA₂DS₂-VASc score[#]	3 [2-4]	3 [2-4]	3 [2-5]	0.038
Time in therapeutic range (%)	65.5±17.3	62.2±17.3	63.6±16.7	0.21
HAS-BLED score[#]	2 [1-2]	2 [1-2]	1 [1-2]	0.001
Arterial Hypertension (treated) (%)	91.5	91.8	95.1	0.18
Diabetes mellitus (%)	19.9	20.0	19.6	0.99
Heart failure (%)	15.5	18.2	19.2	0.49
History of stroke/TIA (%)	15.5	14.6	19.9	0.20
History of MI/ Cardiac Revascularization (%)	21.4	23.6	26.9	0.31
Anti-platelets (%)	9.6	6.1	5.6	0.14

MI: myocardial Infarction, TIA: transient ischemic attack.

[#]data expressed as median and interquartile range.

Table 3. Adjusted hazard ratios, based on a Cox proportional Hazards model according to selected variables.

Panel A. CV Events	p	HR	95%CI	
Age per 1 SD	<0.001	1.72	1.33	2.21
Women	0.26	0.78	0.51	1.20
Arterial Hypertension (treated)	0.63	0.83	0.32	2.14
Diabetes Mellitus	0.005	1.89	1.20	2.96
Smoking	0.26	1.48	0.75	2.90
Heart Failure	0.044	1.60	1.01	2.54
History of Stroke/TIA	0.003	1.96	1.25	3.06
History of MI/Cardiac Revascularization	0.59	1.14	0.71	1.84
Anti-platelets	0.89	1.07	0.41	2.77
Statins	0.83	0.95	0.61	1.49
Urinary 11-dehydro-TxB ₂ per 1SD	<0.001	1.64	1.42	1.89
Time in Therapeutic Range	0.96	0.99	0.98	1.02
Panel B. CV deaths	p	HR	95%CI	
Age per 1 SD	<0.001	2.04	1.43	2.92
Women	0.43	0.79	0.45	1.41
Arterial Hypertension (treated)	0.90	1.10	0.24	4.92
Diabetes Mellitus	0.004	2.43	1.33	4.43
Smoking	0.79	1.16	0.39	3.50
Heart Failure	0.11	1.67	0.90	3.10
History Stroke/TIA	0.022	2.00	1.10	3.63
History of MI/Cardiac Revascularization	0.39	1.33	0.70	2.54
Anti-platelets	0.56	1.44	0.42	4.99
Statins	0.037	0.49	0.25	0.96
Urinary 11-dehydro-TxB ₂ per 1SD	<0.001	1.66	1.36	2.02
Time in Therapeutic Range	0.49	0.98	0.96	1.02

CI: confidence interval, CVE: cardiovascular event, HR: hazard ratios, MI: myocardial Infarction,

TIA: transient ischemic attack, TxB₂: Thromboxane B₂.

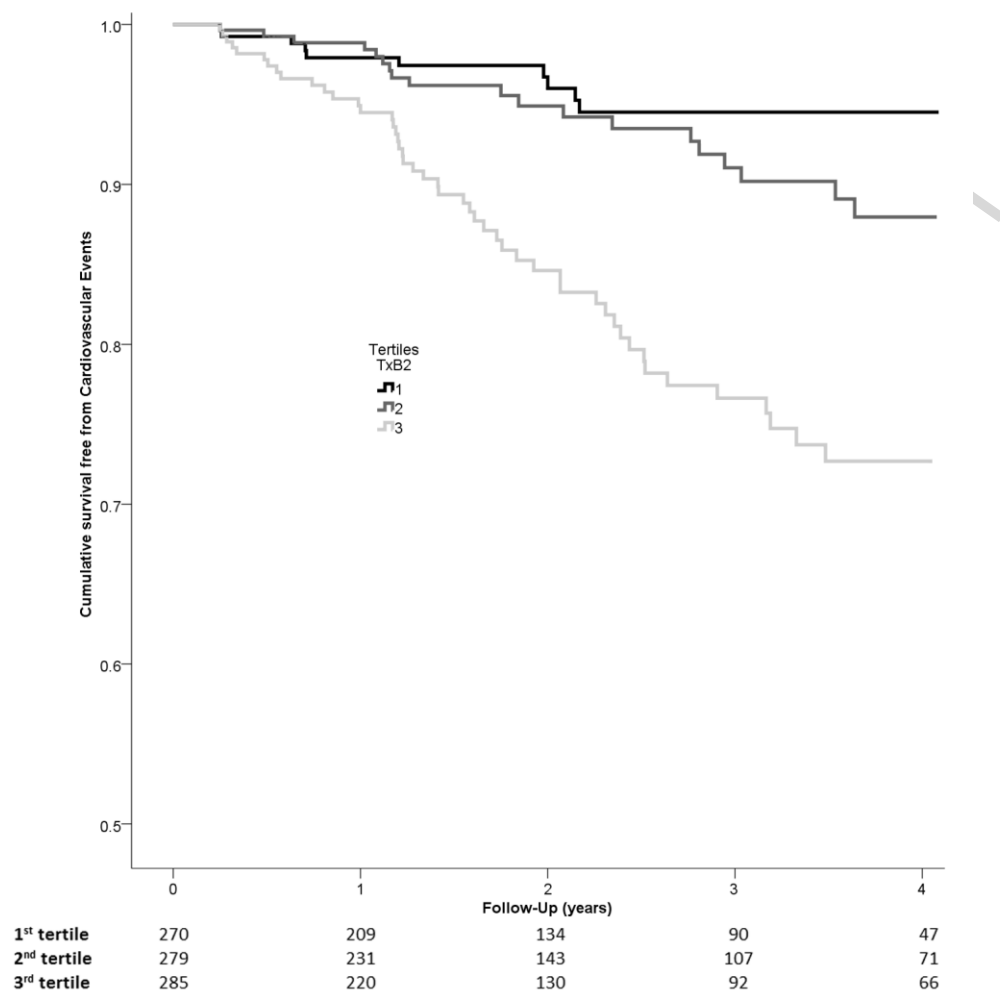


Fig. 1